

# Cancer vaccine

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A **cancer vaccine** is a [vaccine](#) that either treats existing [cancer](#) or prevents development of a cancer. Vaccines that treat existing cancer are known as *therapeutic* cancer vaccines. There are currently no vaccines able to prevent all cancers, however vaccines against some oncoviruses have proven extremely effective.<sup>[1]</sup>

Some [types of cancer](#), such as [cervical cancer](#) and some [liver cancers](#), are caused by viruses (oncoviruses), and traditional vaccines against those viruses, such as [HPV vaccine](#) and [hepatitis B vaccine](#), will prevent those types of cancer. These anti-viral vaccines are not further discussed in the rest of this article. Other cancers are to some extent caused by bacterial infections (e.g. stomach cancer and [Helicobacter pylori](#)<sup>[2]</sup>) and traditional vaccines against cancer-causing bacteria are also not discussed in this article.

Scientists are continuing research and development of vaccines against other types of cancer. Some researchers believe that cancer cells routinely arise and are destroyed by the healthy immune system;<sup>[3]</sup> and that cancer forms when the immune system fails to destroy them.<sup>[4]</sup>

## Method

One approach to cancer vaccination is to separate proteins from cancer cells and immunize cancer patients against those proteins, in the hope of stimulating an immune reaction that could kill the cancer cells. Therapeutic cancer vaccines are being developed for the treatment of breast, lung, colon, skin, kidney, prostate, and other cancers.<sup>[5]</sup>

In a phase III trial of [follicular lymphoma](#) (a type of non-Hodgkin's lymphoma), investigators reported that the [BiovaxID](#) (on average) prolonged remission by 44.2 months, versus 30.6 months for the control, at the June 2009 meeting of the American Society of Clinical Oncology.<sup>[6]</sup>

On April 14, 2009, [Dendreon](#) Corporation announced that their Phase III clinical trial of [Provenge](#), a cancer vaccine designed to treat prostate cancer, had demonstrated an increase in survival. It received [U.S. Food and Drug Administration](#) (FDA) approval for use in the treatment of advanced prostate cancer patients on April 29, 2010.<sup>[7]</sup> The approval of Provenge has stimulated interest in this type of therapy.<sup>[8]</sup>

Another approach to therapeutic anti-cancer vaccination is to generate the immune response *in situ* in the patient using [oncolytic viruses](#). This approach has been successfully used in the drug [talimogene laherparepvec](#), a version of [herpes simplex virus](#)

which has been engineered to replicate selectively in tumor tissue and also to express the immune stimulatory protein GM-CSF. This enhances the anti-tumor immune response to tumor antigens released following viral lysis and provides an *in situ* patient specific anti-tumor vaccine as a result. Interim phase 3 trial results in melanoma showed a significant tumour response rate compared to administration of GM-CSF alone.<sup>[9]</sup>

On April 8, 2008, New York-based company Antigenics announced that it had received approval for the first therapeutic cancer vaccine in Russia. It is the first approval by a regulatory body of a cancer immunotherapy. The treatment, Oncophage, increased recurrence-free survival by a little more than a year according to the results of a phase III clinical trial. The approval is for a subset of kidney cancer patients who are at intermediate risk for disease recurrence. It awaits approval in the US and EU.<sup>[10]</sup> but will need a new trial for FDA approval.

## Companies and vaccine candidates

Most of the cancer vaccines in development are addressing specific cancer types and are therapeutic vaccines. Several cancer vaccines are currently in development by companies such as:

- Aduro (GVAX), formerly being developed by Cell Genesys
- Advaxis<sup>[11]</sup> (ADX11-001, ADX31-001, ADX31-164)
- ALVAC-CEA vaccine
- Avax Technologies [AC Vaccine]
- Amgen (talimogene laherparepvec)
- Accentia Biopharmaceuticals majority owned subsidiary Biovest International (BiovaxID in phase III)
- Bavarian Nordic<sup>[12]</sup> (Prostvac)
- Celldex Therapeutics (CDX110, CDX1307 and CDX1401)
- The Center of Molecular Immunology, based in Cuba, has produced CimaVax-EGF, which targets lung cancer
- CureVac develops mRNA-based cancer immunotherapies; CV9104 is currently being evaluated in an international Phase 2b trial in patients with castration-resistant prostate cancer<sup>[13]</sup>
- Dendreon Corp (DNDN) (Neuvvenge, for HER2/neu expressing cancers such as Breast, Bladder, colon, Ovarian),<sup>[14]</sup>
- Galena Biopharma (NeuVax)
- Generex Biotechnology through its wholly owned immunotherapeutic subsidiary Antigen Express (Ae-37)
- Geron Corporation (GRNVAC1)
- GlaxoSmithKline is working on a vaccine for melanoma targeting MAGE-A3
- GlobeImmune<sup>[15][16]</sup> (Tarmogens, GI-4000, GI-6207, GI-6301)<sup>[17]</sup>
- Heat Biologics ImPACT Therapy against NSCLC and other cancers
- Immatics biotechnologies (e.g. IMA901 for renal cancer)<sup>[18]</sup>

- Immunitor is conducting trials of an oral cancer vaccine, hepcortespenlisimut-L.<sup>[19]</sup> <sup>[20]</sup> A Phase 3 trial in hepatocellular carcinoma was first made public in September 2014.<sup>[21]</sup>
- Merck, in 2009, is starting phase III trials of Stimuvax for breast cancer.<sup>[22]</sup> It had promising results from a phase IIB trial for inoperable lung cancer.
- Northwest Biotherapeutics <sup>[23]</sup>
- Oncotherapy Science (The first world peptide vaccines are produced. Some of vaccines are now in phase 2&3<sup>[24]</sup>)
- Panacela Labs, Inc. a **Cleveland Biolabs (CBLI)** Subsidiary: MOBILAN Adenovirus-based treatment inducing immune response. Ready for final stage of preclinical development.
- Prima BioMed LTD - Cvac, therapy against ovarian cancer in phase III.<sup>[25]</sup>

Regeneus - RGSH4K - A promising innovative personalised cancer immunotherapy

- Scancell Holdings, (SCIB1)
- OncoPep, Inc - PVX-410, (a multi-peptide vaccine) in a phase I/II trial (NCT01758328)<sup>[26]</sup> to treat smoldering multiple myeloma.<sup>[27]</sup>

## Approved therapeutic vaccines

- Antigenics Inc. (Oncophage, approved in Russia in 2008 for kidney cancer),
- Dendreon Corp (Sipuleucel-T, Provenge, FDA approved April 2010 for metastatic hormone-refractory prostate cancer).

## Abandoned

CancerVax (Canvaxin), Genitope Corp (MyVax personalized immunotherapy), and Favrlle Inc (FavId) are examples of cancer vaccine projects that have been terminated due to poor phase III results (despite promising phase II data and strong immune responses).

## Desired characteristics

Effective cancer vaccines must resolve several challenges. Cancer vaccines seek to target an antigen specific to the tumor and distinct from self-proteins. Selection of the appropriate adjuvant, molecules that activate antigen-presenting cells to stimulate immune responses, is required. At the present time, only Bacillus Calmette-Guérin (BCG), aluminum-based salts and a squalene-oil-water emulsion are approved worldwide for clinical use. The effective vaccine also should seek to provide longterm memory to prevent tumor recurrence. Some scientists believe that for total tumor elimination, both the innate and adaptive immune systems should be activated.<sup>[28]</sup>

## Antigen candidates

Tumor antigens have been divided into two broad categories: *shared* tumor antigens; and *unique* tumor antigens. Shared antigens are expressed by many tumors. Unique tumor antigens result from mutations induced through physical or chemical carcinogens; they are therefore expressed only by individual tumors.

In one approach, vaccines contain whole tumor cells, though these vaccines have been less effective in eliciting immune responses in spontaneous cancer models. Defined tumor antigens decrease the risk of autoimmunity but because the immune response is directed to a single epitope, tumors can evade destruction through antigen loss variance. A process called "epitope spreading" or "provoked immunity" may mitigate this weakness, as sometimes an immune response to a single antigen will lead to development of immunity against other antigens on the same tumor.<sup>[28]</sup>

## Hypothesized problems

A vaccine against a particular virus is relatively easy to create. The virus is foreign to the body, and therefore will express antigens that the immune system can recognize. Furthermore, there are usually only a few viable variants of the virus in question. It is very hard to develop vaccines for viruses that mutate constantly such as influenza or HIV.

A tumour can have many different types of cells in it, each with different cell-surface antigens. Furthermore, those cells are derived from the individual with cancer, and therefore display few if any antigens that are foreign to that individual. This makes it difficult for the immune system to distinguish the cancer cells from normal cells. Some scientists believe that Renal cancer and melanoma are the two cancers with most evidence of causing spontaneous and effective immune responses, possibly because they often display antigens that are recognized as foreign. Therefore, many attempts at developing cancer vaccines are directed against these tumors. However, given Dendreon's success in prostate cancer, a disease that never spontaneously regresses, cancers other than melanoma and renal cancer may be equally amenable to immune attack.

However, most clinical trials investigating a cancer vaccine have failed or had very modest responses by standardized oncologic assessment criteria described as the RECIST criteria.<sup>[29]</sup> The precise reasons are unknown, but possible explanations include:

1. Disease stage being treated was too advanced: it is difficult to get the immune system to fight bulky tumor deposits, because tumors actively suppress the immune system using a variety of mechanisms (e.g. secretion of cytokines that inhibit immune activity). The most suitable stage for a cancer vaccine is likely to be early disease, when the tumor volume is low, but the problem there is that clinical trials take upwards of five years and require high numbers of patients to reach measurable end points. The alternative is to target patients with minimal residual disease after de-bulking of the tumor by surgery, radiotherapy or (providing it does not in itself harm the immune system) chemotherapy.
2. Escape loss variants (cancer vaccines that target just one tumor antigen are likely to be less effective. Tumors are highly heterogeneous and antigen expression

differs markedly between tumors (even within deposits in the same patient). The most effective cancer vaccine is likely to raise an immune response against a broad range of tumor antigens to minimise the chance of the tumor being able to mutate and become resistant to the therapy.)

3. Prior treatments (numerous clinical trials in the past have treated patients who have received numerous cycles of chemotherapy. Chemotherapy is often myelosuppressive and destroys the immune system. There is little point giving a cancer vaccine to a patient who is immune suppressed).
4. Some tumors progress very rapidly and/or unpredictably, and they can literally outpace the immune system. It may take two to three months for an immune response to a vaccine to mature, but some cancers (e.g. advanced pancreatic) can produce marked clinical deterioration, or even death, within this timeframe.
5. Many cancer vaccine clinical trials examine immune responses by patients as their primary goal. Correlations are then made, typically showing that the patients who made the strongest immune responses were the ones who lived the longest, and this is taken as evidence that the vaccine is working. The alternative explanation, however, is that the patients who made the best immune responses were the healthier patients with the better prognosis, and they would have survived longest in any event, even without the vaccine. In other words, the immune responses may simply be a simple reflection of a better health status, not an indication that the vaccine had any beneficial effects. As such, these immune 'false friends' may have tempted some to embark on expensive phase III trials without a solid rationale.

## Recommendations for success

In January 2009, a review article was published in *Expert Reviews in Anticancer Therapy* (Vol 9, #1, pages 67–74) which highlighted past program failures and made recommendations for success as follows:

1. Target settings with a low or very low burden of disease; it is clear that vaccines will not work in patients with advanced metastatic disease.
2. Conduct randomized Phase II trials so that the Phase III program is sufficiently powered – resist the temptation to leap into Phase III prematurely.
3. Do not randomize antigen plus adjuvant versus adjuvant alone. The goal is to establish clinical benefit of the immunotherapy (i.e., adjuvanted vaccine) over the standard of care, not over standard of care plus adjuvant. The adjuvant may have a low-level clinical effect that would skew the statistical powering of the trial, increasing the chances of a false negative.
4. Base development decisions on clinical data, not just immune responses. Time-to-event end points are more valuable and clinically relevant. To date, immune responses have not been predictive of clinical benefit. It is possible that the ability to mount an immune response is merely a prognostic factor that identifies patients with pretreatment characteristics that favor longer survival.

5. Regulatory compliance needs to be designed into the program from inception; invest in the manufacturing process and product assays early. It is much more difficult to retrofit.